FACILITIES INSPECTION (EER REPORT)

SEE PAGE 86 OF CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

PAGE (S) 86 WITHHELD

Reason B4 CCI

METHODS VALIDATION

SEE PAGE 84 OF CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

PAGE (S) 84 WITHHELD

Reason B4 CCI

Bradley, Sean

From: Temple, Robert
Sent: Monday, May 12, 2003 5:41 PM
To: Morse, David E
Cc: Bross, Peter F; Rosario, Lilliam; Bradley, Sean
Subject: RE: Velcade Pregnancy labeling

I'm convinced.

-----Onginal Message-----
From: Morse, David E
Sent: Monday, May 12, 2003 4:11 PM
To: Temple, Robert
Cc: Bross, Peter F; Rosario, Lilliam; Morse, David E; Bradley, Sean
Subject: Velcade Pregnancy labeling

Bob

Rick forwarded your inquiry regarding the labeling of Velcade as a Pregnancy Category "D" vs. "C".

To highlight the significant findings:

1) Velcade was embryolethal in rats and rabbits, at doses approximating 1/2 of the clinical dose (based on BSA). Importantly, the embryolethality in the rabbit was seen at doses which were minimally toxic to the does (i.e., caused transiently decreases in food consumption following the initiation of dosing). Higher doses could not be tested due to severe maternal toxicity/lethality. Specifically, pregnant rabbits given PS-341 during organogenesis at a dose of 0.6 mg/m^2 (half the recommended clinical dose) experienced significant post-iinplantation losses and decreased numbers of live fetuses at minimally maternal toxic doses . Live fetuses from these litters also showed significant decreases in fetal weight. However, PS-341 was not teratogenic in rats and rabbits at the highest dose tested (0.5mg/m^2 and 0.6 mg/m^2, respectively) when administered during organogenesis.

2) While no formal transplacental transfer studies were performed, tissue distribution studies in the rodent suggest that PS-341 is freely capable of crossing vascular and cellular membranes without need of a specific transport mechanism. Moreover, the binding of PS-341 within tissues was far in excess of plasma concentrations throughout the distribution and elimination phases of drug handling. Thus, there is reason to suspect that exposure of the developing fetus to PS-341 will occur, and at levels in excess of plasma drug concentrations.

3) PS-341 has the specific activity of inhibiting the chymotryptic activity of the 26S proteosome, resulting in cell cycle arrest in proliferating cells, and the induction of apoptosis. While the data are somewhat unclear, the toxicity profile for PS-341 suggest that many of the end-organ toxicities seen following treatment predominate in tissues with high proliferation rates. Thus, the likelihood of a perturbation to scheduled cell death (apoptosis) among the rapidly proliferating cells/tissues of the developing fetus appears a high probability event.

4) While not a 'classic' cytotoxic agent (i.e., a nucleoside analog or interchelator), the functional result of PS-341 inhibition of the proteosome is cellular death/apoptosis. The division has considerable experience with such compounds, and has invariably considered these agents to represent a significant risk to the developing fetus (either as a teratogen or as a fetotoxic/embryolethal agent). Such compounds have generally been labeled as Pregnancy category "D".

5) Pregnancy Category D is based on adverse effects on the fetus, which must include embryolethality effects and the continuation/discontinuation of pregnancy (or the abrupt and unscheduled end of pregnancy).

To summarize- PS-341 was embryolethal at fractions of the human dose and with minimal toxicity to the dam; exposure of the fetal tissue to PS-341 is highly likely; PS-341 causes apoptosis of proliferating cells (and perhaps non-proliferating cells); and the PS-341 toxicity profile is generally similar to many cytotoxic compounds which are labeled as Pregnancy category "D".

David

CC: Lilliam Rosario, P/T Reviewer for Velcade

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIO-RENAL DRUG PRODUCTS

FROM: Anthony G. Proakis, Ph.D., Pharmacologist Reviewer, DCRDP, HFD-110

THROUGH: Charles A. Resnick, Ph.D., Pharmacology Team Leader, DCRDP, HFD-110
Douglas C. Throckmorton, M.D., Director, DCRDP, HFD-110

TO: Richard Pazdur, M.D., Director, Div. Oncology Drug Products, HFD-150
Sean Bradley, Project. Manager, Div Oncology Drug Products, HFD-150
Sandi Leigh Verbois, Ph.D. Div. Oncology Drug Products, HFD-150

SUBJECT: Velcade Inj. (PS-341, Millennium Pharmaceuticals); NDA #21,602

DATE RECEIVED: 2/20/03
DATE COMPLETED: 4/01/03

INTRODUCTION

Millennium Pharmaceuticals submitted to the Division of Oncology Drug Products a New Drug Application (NDA # 21,602) for Velcade (bortezomib) for Injection for the treatment of relapsed/refractory multiple myeloma

The Division of Oncology Drug Products is requesting that we evaluate the results of non-clinical pharmacology studies, conducted in cynomolgus monkeys, that showed increases in myocardial contractility at doses that are clinically relevant.

Three study reports were submitted that describe the effects of PS-341 on cardiovascular function in cynomolgus monkeys.

STUDY DESCRIPTIONS AND RESULTS

PS-341: Cardiovascular Effects after Intravenous Administration in Telemetered Cynomolgus Monkeys

This study, conducted for Millennium Pharmaceuticals by [redacted], assessed the effects of single intravenous doses of PS-341 in cynomolgus monkeys. One male and one female monkey each received an intravenous dose of 0.2 mg PS-341/kg on Day 1 of the study and a second intravenous dose of 0.3 mg PS-341/kg on Day 32 of the study. The animals were monitored for clinical signs of toxicity at periodic intervals following each dose. Electrocardiographic (Lead II) and blood pressure measurements were recorded telemetrically before each dose and continuously for up to 24 hours after the 0.2 mg/kg dose and for 12 hours after the 0.3 mg/kg dose. Approximately 12 hours after the second dose, the animals were sacrificed and necropsied.

The administration of the 0.2 mg/kg IV dose resulted in vomiting by the female monkey approximated 6 hours after dosing on Day 1; the 0.3 mg/kg dose resulted in vomiting approximately 6 hours after dosing in the male monkey and on six occasions (approximately 4.5 to 11 hours postdose) for the female monkey.

Heart rates and mean blood pressures (results presented as continuous recordings) fluctuated during the predose and post dose periods. A sustained fall in mean blood pressure (~ 20 mmHg) accompanied by a rise in heart rate (~ 40-50 bpm) occurred in the female monkey approximately 6 hours after the 0.2 mg/kg dose. The cardiovascular responses in the female monkey appeared to coincide with the emetic episode in

this animal. It is not discernable if the cardiovascular responses were direct effects of the drug or were physiological consequences of the emetic response. A similar delayed blood pressure fall and heart rate increase was seen in this animal following the 0.3 mg/kg dose. Heart rate and blood pressure in the male did not seem to be remarkably changed from predose values following either dose of PS-341.

Cardiotoxicity of PS-341(NSC-D681239) in the Monkey

This study was conducted for the National Cancer Institute, NIH, [redacted] to evaluate the potential cardiotoxicity of intravenous doses of PS-341 in male cynomolgus monkeys. Four monkeys were administered a single IV dose of PS-341 (0.1, 0.2, 0.25 or 0.3 mg/kg) and the animals were observed for clinical signs of toxicity up to 12 hours postdose and then twice daily for up to 8 days postdose. Heart rate, blood pressures, body temperature and ECGs were recorded from all animals via implanted radiotelemetry devices.

The 0.1 mg/kg dose elicited no adverse effects. The monkey given the 0.2 mg/kg dose vomited approximately 6 hours after dosing. After the 0.25 mg/kg dose, the animal vomited approximately 4.5 and 5.5 hours postdose. The fourth animal, which received the 0.3 mg/kg dose, became lethargic experienced neuromuscular tremors, developed diarrhea, laid down in its cage and became unresponsive. The latter two animals given the 0.25 and 0.3 mg/kg doses were euthanized approximately 13-14 hours following dosing.

Heart rates increased in all 4 animals following administration of PS-341. The mean blood pressure in the animal given the 0.1 mg/kg dose showed little to no change from predose levels; however, a fall in mean blood pressure was observed after administration of 0.2, 0.25 and 0.3 mg/kg of PS-341. Blood pressure returned to normal levels after the 0.2 mg/kg dose but did not follow diurnal patterns for approximately 4 to 5 days after dosing. The elevated heart rate seen with 0.1 and 0.2 mg/kg returned to baseline after 2 to 4 days post dose. The animal receiving the highest dose became extremely hypotensive and remained so until euthanized. No effect on the electrocardiogram was seen following any dose of PS-341.

It appears that the increased heart rate following PS-341 administration is a compensatory response to the drug-induced hypotension.

A Study to Determine the Effects of PS-341 on Cardiovascular Function after Intravenous Administration to Anesthetized Cynomolgus Monkeys

This study was conducted for Millennium Pharmaceuticals by [redacted] to evaluate the effects of intravenous PS-341 on cardiovascular function in anesthetized cynomolgus monkeys. Three male and three female cynomolgus monkeys were anesthetized with isoflurane and instrumented to record heart rate, arterial blood pressure, pulmonary arterial blood pressure, central venous pressure, left ventricular pressure and contractility (LVdp/dt), cardiac output body temperature and electrocardiogram. Single PS-341 doses of 0.03, 0.3 and 0.5 mg/kg were administered intravenously to 1M and 1F per dose. The animals were monitored for 6 hours after dosing. Venous blood samples were obtained at baseline and one and six hours post dose for measurement of plasma concentrations of PS-341.

No animals died during the 6-hour postdose observation period. The electrocardiogram was unaffected by PS-341 treatment. At the 0.03 mg/kg dose, heart rates fluctuated ± 10% from mean baseline values over the 6-hour period. This dose induced a gradual increase (10-25%) in blood pressure that peaked at 3 to 4 hours following dosing. At the 0.3 mg/kg dose, both animals experienced an initial decrease (10-20%) in arterial pressure during the first hour after dosing with blood pressure continuing to decline over the 6 hour observation period. Heart rate in the male at the 0.3 mg/kg dose increased gradually and at 5 hours post dose was about 50% higher than baseline value. Heart rate in the female treated with 0.3 mg/kg of PS-341 increased modestly (~10%). In both animals given the 0.5 mg/kg dose, a biphasic blood pressure response was observed, an initial increase (30-50%) above baseline value during the first 2 hours post dose followed by a decrease in blood pressure from baseline. Heart rate in the male monkey showed a gradual decrease

(~10%) over the 6 hours period whereas a gradual increase (up to 40% from baseline) was seen in the female given the 0.5 mg/kg dose.

Maximal LVdp/dt increased by 20-50% above baseline in both animals given the 0.03 mg/kg dose and increased up to 300% above baseline in both males and females after the 0.3 mg/kg and 0.5 mg/kg doses.

Cardiac output remained relatively unchanged in each animal after the 0.03 mg/kg dose but increased above baseline values after the 0.3 and 0.5 mg/kg doses.

SUMMARY AND EVALUATION

In the two studies conducted in conscious cynomolgus monkeys, a steep dose-response for toxicity was observed for PS-341. No adverse effects were observed after an IV dose of 0.1 mg PS-341/kg. Doses ≥ 0.2 mg/kg IV caused emesis and a dose of 0.3 mg/kg IV produced neuromuscular tremors, diarrhea and unresponsiveness that necessitated early sacrifice of the animals.

In conscious monkeys, IV doses ≥ 0.2 mg PS-341/kg caused a drop in mean arterial blood pressure and increases in heart rates from baseline levels. The increases in heart rate generally coincided with the blood pressure fall and appears to reflect a compensatory response to the drug-induced hypotension.

In anesthetized monkeys, doses up to 0.5 mg/kg of PS-341 (which were emetic in conscious animals) were explored for effects on cardiovascular function without causing vomiting. The lowest dose (0.03 mg/kg IV) produced minor fluctuations in mean blood pressures and heart rates. A reduction in mean blood pressure from baseline level occurred in the male and female monkeys treated with the 0.3 mg/kg IV dose and was accompanied by increases (50% in the male and 10% in the female) in heart rates from baseline. Myocardial contractility (LV dp/dt) in anesthetized monkeys (not measured in conscious animals) increased above baseline after the 0.3 and 0.5 mg/kg doses of PS-341.

A consistent finding among these 3 studies is that PS-341 causes a fall in mean blood pressure following IV doses ≥0.2 mg/kg . The increases in heart rate and myocardial contractility appear to coincide temporally with the induced hypotension and most likely reflect compensatory cardiovascular responses. However, a direct (positive inotropic) effect of PS-341 on the myocardium cannot be totally excluded by these experiments alone. Typically, in vitro isolated heart or isolated myocardial preparations are used to determine direct inotropic (positive or negative) effects of drugs.

HFD-150/Division Files
HFD-110
HFD-110/CResnick
HFD-110/DThrockmorton

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Anthony Proakis
4/3/03 10:10:18 AM
PHARMACOLOGIST

Charles Resnick
4/8/03 04:53:06 PM
PHARMACOLOGIST

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO HFD-110/WLAIL

FROM HFD-150/SVERBOIS/SBRADLEY

)ATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
20FEB03		21-602	NEW NDA	21JAN03

NAME OF DRUG	PRIORITY	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
VELCADE (bortezomib) for INJECITON	CONSIDERATION STANDARD	PROTEASOME INHIBITOR	MARCH 21, 2003

NAME OF FIRM MILLENNIUM PHARMACEUTICALS

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURINGCHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER (fax)
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS OTHER

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below)*
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Changes in some of the parameters measured warrant further investigation, such as 300-400% increase in contractility in doses that are clinically relevant.

1. 6837- 113: PS- 341: Cardiovascular Effects after Intravenous Administration in Telemetered Cynomolgus Monkeys
2. G465502A: Cardiotoxicity of PS-341 (NSC- D681239) in the Monkey (G465502A)
3. KLAW- 191: A study to determine the effects of PS- 341 on cardiovascular function after intravenous administration to anesthetized cynomolgus monkeys

This information can be found in \\CDSESUB1\N21602\N_000\2003-01-21; Module 4: Safety Pharmacology, in folder 4213.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY *(Check one)*
SEAN BRADLEY	☐ MAIL ✗ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER SEAN BRADLEY

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sean Bradley
2/20/03 09:42:01 AM

APPEARS THIS WAY
ON ORIGINAL

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-602	Efficacy Supplement Type SE-	Supplement Number N-000
Drug: VELCADE (bortezomib) for Injection	Applicant: Millennium Pharmaceuticals, Inc.	
RPM: Bradleys, Sean K.	HFD-150	Phone # 301-594-5770
Application Type: (X) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	( ) Standard (X) Priority
• Chem class (NDAs only)	Proteasome Inhibitor
• Other (e.g., orphan, OTC)	Orphan
❖ User Fee Goal Dates	21JUL03
❖ Special programs (indicate all that apply)	( ) None Subpart H (X) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) (X) Fast Track (X) Rolling Review
❖ User Fee Information	
• User Fee	( ) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	(X) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
❖ Exclusivity Summary (approvals only)	X
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	06MAR03

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	( ) Materials requested in AP letter (X) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None (X) Press Release ( ) Talk Paper (X) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	24MAR03 12MAY03
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	----------
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	----------
• Applicant proposed	X
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	X
• Documentation of discussions and/or agreements relating to post-marketing commitments	X
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	04SEP02
• Pre-NDA meeting (indicate date)	02DEC02
• Pre-Approval Safety Conference (indicate date; approvals only)	08MAY03
• Other	----------
❖ Advisory Committee Meeting	
• Date of Meeting	----------
• 48-hour alert	----------
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	

Clinical and Summary Information	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	09MAY03-Team Leader 13MAY03-Division Director
❖ Clinical review(s) *(indicate date for each review)*	09MAY03
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	09MAY03-Section VI clinical rev
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	09MAY03-Section VII clinical rev
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	----------
❖ Statistical review(s) *(indicate date for each review)*	09MAY03-Section VI clinical rev
❖ Biopharmaceutical review(s) *(indicate date for each review)*	12MAY03
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	----------
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	17APR03
• Bioequivalence studies	----------
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	12MAY03-----
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	12MAY03
• Review & FONSI *(indicate date of review)*	12MAY03
• Review & Environmental Impact Statement *(indicate date of each review)*	12MAY03
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	02MAY03
❖ Facilities inspection (provide EER report)	Date completed: 08MAY03 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	(X) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	06MAY03
❖ Nonclinical inspection review summary	----------
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	----------
❖ CAC/ECAC report	----------

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved OMB No 0910-0297
Expiration Date. February 29, 2004

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1 APPLICANT'S NAME AND ADDRESS

Millennium Pharmaceuticals, Inc.
75 Sidney Street
Cambridge, MA 02139
USA

2 TELEPHONE NUMBER *(Include Area Code)*

(617) 679-7000

3 PRODUCT NAME

VELCADE™ (bortezomib) for Injection

4 BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA Number 21-602

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

[X] YES [ ] NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW.

[X] THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

[ ] THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I D. NUMBER

4489

7 IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION

[ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

[ ] A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box)*

[ ] THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box)*

[ ] THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box)*

[ ] THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8 HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? [ ] YES [X] NO

(See Item 8, reverse side if answered YES)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	**Vice President, Worldwide Regulatory Affairs & Pharmacovigilance**	Dec. 30, 2002

FORM FDA 3397 (4/01)

DEPARTMENT OF
HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville MD 20857

1f35

Official Business
Penalty For Private Use $300

ROCKVILLE MD JAN 15'03

U.S. OFFICIAL MAIL
PENALTY FOR PRIVATE USE $300
PB METER 7249594
=060=
U.S. POSTAGE

Tanya Lewis, MS
Senior Manager, Reg Affairs
Millennium Pharmaceuticals, Inc.
75 Sidney Street
Cambridge, MA 02139

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-602	Efficacy Supplement Type SE-	Supplement Number N-000
Drug: VELCADE (bortezomib) for Injection	Applicant: Millennium Pharmaceuticals, Inc.	
RPM: Bradleys, Sean K.	HFD-150	Phone # 301-594-5770
Application Type: (X) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	( ) Standard (X) Priority
• Chem class (NDAs only)	Proteasome Inhibitor
• Other (e.g., orphan, OTC)	Orphan
❖ User Fee Goal Dates	21JUL03
❖ Special programs (indicate all that apply)	( ) None Subpart H (X) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) (X) Fast Track (X) Rolling Review
❖ User Fee Information	
• User Fee	( ) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	(X) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
❖ Exclusivity Summary (approvals only)	X
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	06MAR03

General Information	
Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	( ) Materials requested in AP letter (X) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None (X) Press Release ( ) Talk Paper (X) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	X
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	----------
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	----------
• Applicant proposed	X
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	X
• Documentation of discussions and/or agreements relating to post-marketing commitments	X
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	04SEP02
• Pre-NDA meeting (indicate date)	02DEC02
• Pre-Approval Safety Conference (indicate date; approvals only)	08MAY03
• Other	----------
❖ Advisory Committee Meeting	
• Date of Meeting	----------
• 48-hour alert	----------
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	

Clinical and Summary Information	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	09MAY03-Team Leader
❖ Clinical review(s) *(indicate date for each review)*	09MAY03
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	09MAY03-Section VI clinical rev
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	09MAY03-Section VII clinical rev
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	----------
❖ Statistical review(s) *(indicate date for each review)*	09MAY03-Section VI clinical rev
❖ Biopharmaceutical review(s) *(indicate date for each review)*	12MAY03
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	----------
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	17APR03
• Bioequivalence studies	----------
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	Pending------
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	02MAY03
❖ Facilities inspection (provide EER report)	Date completed: 08MAY03 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	(X) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	06MAY03
❖ Nonclinical inspection review summary	----------
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	----------
❖ CAC/ECAC report	----------

EXCLUSIVITY SUMMARY for NDA # 21-602

Trade Name VELCADE Generic Name bortezomib

Applicant Name Millennium Pharmaceuticals, Inc. HFD- 150

Approval Date 13MAY03

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES /_X__/ NO /___/

b) Is it an effectiveness supplement? YES /___/ NO /___/

If yes, what type(SE1, SE2, etc.)?

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES /_X__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /__/ NO /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_X__/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /_X__/
Investigation #3	YES /___/	NO /_X__/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X__/

Investigation #3 YES /___/ NO /_X__/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # M34100-024

Investigation #__, Study # M34100-025

Investigation #__, Study # LCCC 9834/00-31

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND ——— YES /_X__/	NO /___/ Explain:
Investigation #2	
IND #——— YES /__X_/	NO /___/ Explain:
Investigation #2	
IND #——— YES /_X__/	NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

Investigation #2	!	
YES /___/ Explain _____	!	NO /_X__/ Explain _____
_____	!	_____
_____	!	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____
Signature of Preparer Date
Title: Regulatory Health Project Manager

Signature of Office or Division Director Date

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Richard Pazdur
5/13/03 02:37:38 PM

APPEARS THIS WAY
ON ORIGINAL

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA Number: **21-602**

Requested Trade Name: **VELCADE™ for Injection**

Generic Name and Strengths: **bortezomib/3.5 mg**

Applicant: **Millennium Pharmaceuticals, Inc.**

Date of Application: **January 21, 2003**
Date of Receipt: **January 24, 2003**
Date of Filing Meeting: **March 5, 2003**
Filing Date: **March 22, 2003**

Indication(s) requested: Treatment of relapsed or refractory multiple mylema

Type of Application: Full NDA __X_____ Supplement _____
(b)(1) _____X_____ (b)(2) _____
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S_____ P__X_____
Resubmission after a withdrawal or refuse to file _____
Chemical Classification: (1,2,3 etc.)__1P__
Other (orphan, OTC, etc.)__ORPHAN_____

Has orphan drug exclusivity been granted to another drug for the same indication? **NO**

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

If the application is affected by the application integrity policy (AIP), explain.

User Fee Status: Paid _____ Waived (e.g., small business, public health) _____
Exempt (orphan, government) __ORPHAN_____
Form 3397 (User Fee Cover Sheet) submitted: **YES**_____
User Fee ID#__4489_____
Clinical data? YES __X____ NO _____ Referenced to NDA# _____
Date clock started after UN _____

User Fee Goal date: ____**JULY 21, 2003**_____

Action Goal Date (optional) _____

- Does the submission contain an accurate comprehensive index? **YES**

- Form 356h included with authorized signature? **YES**
- **If foreign applicant, the U.S. Agent must countersign.**

Submission complete as required under 21 CFR 314.50? **YES**

- If electronic NDA, does it follow the Guidance? **YES**
  If an electronic NDA: all certifications must be in paper and require a signature.

- If Common Techinical Document, does it follow the guidance? **YES**

- Patent information included with authorized signature? **YES**

- Exclusivity requested? **YES**; If yes, _____years
  Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? **YES**
  If foreign applicant, the U.S. Agent must countersign.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, ..."

- Financial Disclosure included with authorized signature? **YES**
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign.

- Has the applicant complied with the Pediatric Rule for all ages and indications? **YES**
  If no, for what ages and/or indications was a waiver and/or deferral requested:

- Field Copy Certification (that it is a true copy of the CMC technical section)? **YES**

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? **YES**
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? **YES**

List referenced IND numbers: ———

End-of-Phase 2 Meeting? Date: **September 4, 2002**
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? Date: **December 2, 2002**
If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI) sent to DDMAC? **YES**

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support? **YES**

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support? **NA**

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? **NA**

Advisory Committee Meeting needed? **NO**

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? **NO**

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? **YES**
  If no, did sponsor submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO
- Establishment Evaluation Request (EER) package submitted? **YES** NO
- Parenteral Applications Consulted to Sterile Products (HFD-805)? **NO**

If 505(b)(2), complete the following:

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)? (Normally, FDA will refuse-to-file such applications.) YES NO

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?
If yes, the application must be refused for filing under 314.54(b)(1) YES NO

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? YES NO

If yes, the application must be refused for filing under 314.54(b)(2)

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

____ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

  YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  YES NO

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 6, 2003

BACKGROUND:

VELCADE™ (bortezomib) for Injection, formerly known as PS-341, is developed by Millennium Pharmaceuticals, Inc., as a potent and reversible proteasome inhibitor. It is a novel cytotoxic chemical entity which acts as a potent, selective and reversible inhibitory of the 26S proteasome. VELCADE™ studies have been under the review of the Division of Oncology Drug Products under IND.

ATTENDEES:

Richard Pazdur, M.D.	Division Director
Grant Williams, M.D.	Deputy Division Director
Lillia Talarico, M.D.	Associate Director
Ann Farrell, M.D.	Acting Medical Team Leader
Peter Bross, M.D.	Medical Reviewer
Robert Kane, M.D.	Medical Reviewer
Sophia Abraham, Ph.D.	Biopharm Reviewer
Dave Morse, Ph.D.	Pharm/Tox Team Leader
Lilliam Rosario, Ph.D.	Pharm/Tox Reviewer
William McGuinn, Ph.D.	Pharm/Tox Reviewer
Sean Bradley, R.Ph.	Consumer Safety Officer

ASSIGNED REVIEWERS:

Discipline	Reviewer
Medical:	Peter Bross, MD
Secondary Medical:	Robert Kane, MD
Statistical:	Yong-Cheng Wang, PhD
Pharmacology:	Lilliam Rosario, PhD
Chemist:	Chengyi Liang, PhD
Biopharmaceutical:	Sophia Abraham, PhD
Microbiology, sterility:	Bryan Riley, PhD
DSI:	Khin U, PhD
Project Manager:	Sean Bradley, RPh
Consultants:	
DDMAC Consultant:	Joseph Grillo, Pharm.D.
DDMAC Consultant:	Catherine Miller, Pharm. D.
ODAC Consultant:	Chatchada Karanes, MD
ODAC Consultant:	Harvey Katsen, MD
ODAC Consultant (pending):	Donna Przepiorka, M.D.
Patient Consultant (pending):	Michael Katz

Per reviewers, all parts in English, or English translation? YES__X___ NO___

CLINICAL – File ___X_____ Refuse to file _____

- Clinical site inspection needed: YES___X_____ NO_____

MICROBIOLOGY CLINICAL – File____X_____ Refuse to file_____

STATISTICAL – File ____X_____ Refuse to file _____

BIOPHARMACEUTICS – File ____X_____ Refuse to file _____

- Biopharm. inspection Needed: YES_____ NO ___X_____

PHARMACOLOGY – File ____X_____ Refuse to file _____

CHEMISTRY –

- Establishment(s) ready for inspection? YES __X__NO_____
  File__X___ Refuse to file _____

REGULATORY CONCLUSIONS/DEFICIENCIES:

___X____The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ The application is unsuitable for filing. Explain why:

Sean K. Bradley, R.Ph.

Regulatory Project Manager, HFD-150

FILING MEETING

NDA# 21-602 Date: March 5, 2003

Date Received: January 21, 2003 **PDUFA Due Date:** July 21, 2003

Drug Name: VELCADE (bortezomib) for Injection

Sponsor: Millennium Pharmaceuticals

Proposed Indication: Treatment of relapsed or refractory multiple mylema

Attendees:

Clinical:	Bross/Kane/Farrell
Pharm/Tox:	Rosario/McGuinn/Morse
Biopharmaceutical:	Abraham

Discussion Points

1. Clinical (Bross/Kane/Farrell)

   - 202 patients to review
   - there is no available bridging data set

2. Statistical (Wang/Chen)

   No filing issues

3. Pharmacolgy/Toxicology

   Review assignments:

General Pharm., Mech. of Action, Lit. regarding prion disease -	David McGuinn
Safety Pharmacology -	Leigh Verbois
Pharmacokinetics, Toxicokinetics and ADME -	Anwar Goheer
Genotoxicity -	Shwu-Luan Lee
General Toxicology -	Margot Brower
Reproductive Toxicology -	Kim Benson
Integrated Summary and Final Label -	Lilliam Rosario

   - There is a possible relationship between the neurotoxicity and the cardiotoxicity. There is no "wash-out" period after the drug has been stopped.
   - We will have Phase 4 comments for the sponsor available at sign-off.

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS: HFD-420)

DATE RECEIVED: 1/29/03	DUE DATE: 5/9/03	ODS CONSULT #: 03-0036

TO:

Richard Pazdur, M.D.
Director, Division of Oncology Drug Products
HFD-150

THROUGH:

Sean Bradley
Project Manager, Division of Oncology Drug Products
HFD-150

PRODUCT NAME:	**NDA SPONSOR:** Millennium Pharmaceutical, Inc.
Velcade (Bortezomib for Injection) 3.5 mg **NDA #:** 21-602	

SAFETY EVALUATOR: Jennifer Fan, Pharm.D.

SUMMARY: In response to a consult from the Division of Oncology Drug Products (HFD-150), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name, Velcade, to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATIONS:

1. DMETS has no objection to the use of the proprietary name, Velcade. This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.
2. DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name, Velcade, acceptable from a promotional perspective.

Carol Holquist, R.Ph.
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: May 5, 2003

NDA NUMBER: 21-602

NAME OF DRUG: Velcade (Bortezomib for Injection) 3.5 mg

NDA HOLDER: Millennium Pharmaceuticals, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Oncology Drug Products (HFD-150) for assessment of the tradename, Velcade, regarding potential name confusion with other proprietary and established drug names. Container label and carton labeling were also submitted by the sponsor and reviewed by DMETS.

PRODUCT INFORMATION

Velcade is the proprietary name for bortezomib. It is a proteasome inhibitor and is indicated for the treatment of relapsed and refractory multiple myeloma. The most commonly reported adverse events were nausea, fatigue, diarrhea, constipation, thrombocytopenia, pyrexia, vomiting, anorexia, peripheral neuropathy (including aggravated), and peripheral sensory neuropathy. The recommended dose of Velcade is 1.3 mg/m^2/dose administered as a bolus intravenous injection twice weekly for two weeks. It is administered on days 1, 4, 8, and 11 followed by a 10-day rest period on days 12 through 21. Velcade is available for intravenous injection as a sterile lyophilized powder in single-dose vials containing 3.5 mg of the active ingredient as well as 35 mg of mannitol as an inactive ingredient. Velcade must be reconstituted with 3.5 mL of 0.9% sodium chloride injection, USP.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound alike or look alike to Velcade to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[4] and the data provided by Thomson & Thomson's

[1] MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.
[4] WWW location http://www.uspto.gov.

SAEGIS™ Online Service[5] were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Velcade. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel had sound and look-alike concerns with Veltane (Brompheniramine Maleate). This product is listed in Table 1 (see below), along with the dosage forms available and usual dosage. However, since Veltane is no longer marketed, it will not be discussed in the review.

2. DDMAC finds the proprietary name, Velcade, acceptable from a promotional perspective.

3. Through independent review, DMETS also identified Alcaine as having sound-alike qualities to Velcade. This product is listed in Table 1 (see below).

Table 1

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Velcade	Bortezomib (Rx) Injection: 3.5 mg	1.3 mg/m^2/dose administered as a bolus intravenous injection twice weekly for two weeks on days 1, 4, 8, and 11 followed by a 10-day rest period on days 12 through 21.	
Veltane	Brompheniramine Maleate (Rx) No longer marketed in the U.S.	N/A	SA/LA
Alcaine	(Proparacaine Hydrochloride) (Rx) Solution/Drops (Ophthalmic): 0.5%	*Deep anesthesia* Instill 1 drop every 5 to 10 minutes for 5 to 7 doses *Removal of sutures, foreign bodies* Instill 1 or 2 drops 2 or 3 minutes before removal. *Tonometry* Instill 1 or 2 drops immediately before	SA

[5] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

Product Name	Dosage form(s). Generic name	Usual adult dose*	Other**
Velcade	Bortezomib (Rx) Injection: 3.5 mg	1.3 mg/m^2/dose administered as a bolus intravenous injection twice weekly for two weeks on days 1, 4, 8, and 11 followed by a 10-day rest period on days 12 through 21.	
		measurement.	
*Frequently used, not all-inclusive. **SA (sound-alike), LA (look-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

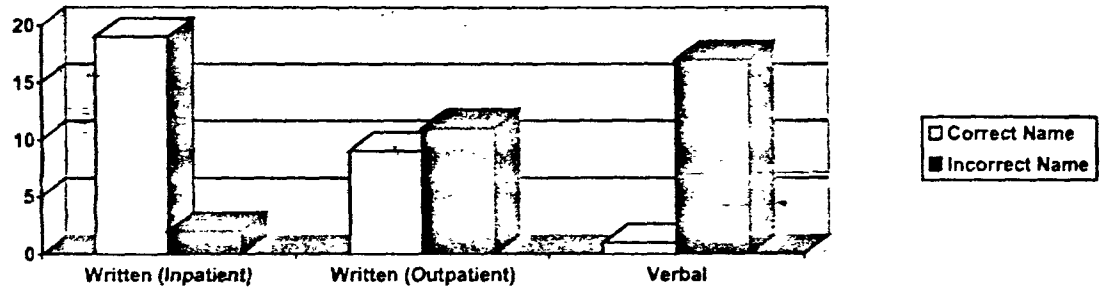
Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Velcade with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 104 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Velcade (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Inpatient Rx: Velcade 2mg IV X 1	*Outpatient Rx:* Velcade 2 mg IV as directed times one today #1.
Outpatient Rx: Velcade Sig: 2mg IV as dir x Today #1	

2. Results:

Results of these exercises are summarized below:

Study	# of Participants	# of Responses (%)	Correctly Interpreted "Velcade"	Incorrectly Interpreted
Written Inpatient	31	21 (68%)	19 (90%)	2 (10%)
Written Outpatient	39	20 (51%)	9 (45%)	11 (55%)
Verbal: Outpatient	34	18 (53%)	1 (6%)	17 (94%)
Total	104	59 (57%)	29 (49%)	30 (51%)



Among the written inpatient prescriptions, 2 (10%) out of 21 respondents interpreted Velcade incorrectly. Misinterpretations included [redacted] (1 respondent, 5%) and [redacted] (1 respondent, 5%). None of the respondents interpreted Velcade as an existing U.S. marketed drug product.

Among the written outpatient prescriptions, 11 (55%) out of 20 respondents interpreted [redacted] incorrectly. Misinterpretations included [redacted] (9 respondents, 45%). [redacted] (1 respondent, 5%), and [redacted] (1 respondent, 5%). None of the respondents interpreted Velcade as an existing U.S. marketed drug product.

Among the verbal outpatient prescriptions, 17 (94%) out of 18 respondents interpreted Velcade incorrectly. Misinterpretations included [redacted] (2 respondents, 11%), [redacted] 2 respondents, 11%) [redacted] 2 respondents, 11%), [redacted] (2 respondents, 11%), [redacted] (1 respondent, 5%), [redacted] (1 respondent, 5%) [redacted] 1 respondent, 5%) [redacted] 1 respondent, 5%), [redacted] (1 respondent, 5%) [redacted] (1 respondent, 5%), [redacted] 1 respondent, 5%). [redacted] (1 respondent, 5%), and [redacted] (1 respondent, 5%). None of the respondents interpreted Velcade as an existing U.S. marketed drug product.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Velcade, the primary concern raised was related to the sound-alike, look-alike name Alcaine, that already exists in the U.S. marketplace.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that Velcade can be confused with other U.S. marketed drug products. The interpretations from the verbal and written prescription studies were phonetic/misspelled variations of the drug name, Velcade. However, a negative finding does not discount the potential for name confusion given the limited predictive value of these studies, primarily due to the sample size.

Velcade sounds similar to Alcaine. Alcaine contains 0.5% proparacaine hydrochloride and is used as an ophthalmic local anesthetic. The "elcade" portion of Velcade sounds similar to Alcaine. The "v" sound in Velcade may distinguish it from Alcaine; however, in the verbal portion of the studies conducted by DMETS, four respondents (22%) interpreted Velcade as Alkaid, Alcade, and Alcaid, which are similar in sound to Alcaine. Two other respondents interpreted Velcade as Elkaid, where the "v" in Velcade was not heard. Even though Velcade and Alcaine may sound similar and are only available in one strength, these drug products differ in dosage form (lyophilized powder that needs to be reconstituted vs. ophthalmic solution), route of administration (parenteral vs. ophthalmic), expression of strength (mg vs. %), and directions of use (twice weekly on days 1, 4, 8, and 11 vs. 1 drop every 5 to 10 minutes or 1 or 2 drops before procedure). Even though Alcaine can be dispensed in an outpatient as well as an inpatient setting, the environment of where these two drug products are administered in is quite different (oncology clinic vs. eye clinic or a physician's office). A physician would immediately realize if he or she received the wrong drug product since one product must be reconstituted and injected while the other one is in a dropper container for the eye. These differences would decrease the risk of a potential medication error occurring between these two drug products.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the draft container labels, carton labeling, and the package insert of Velcade, DMETS has focused on safety issues relating to possible medication errors, and has identified the following areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL (3.5 mg)

1. The "3.5 mg" which appears directly under the NDC number should be deleted.
2. If space permits, directions for reconstitution of the drug product should appear on the label.
3. The total volume and final concentration after reconstitution should also appear on the label.
4. The statement "for injection" should appear in the same font size as the established name.
5. The statement "(bortezomib) for injection" should be revised to state "(bortezomib for injection)".

6. [redacted]

B. PROTECTIVE WRAP

See comment A-4.

C. CARTON LABELING (1 x 3.5 mg)

1. See comment A-4 and A-5.

2. [redacted]

3. [redacted]

4.

5.

6.

7.

D. PACKAGE INSERT LABELING

1. Under the DESCRIPTION section, the statement ".. [redacted] ...leads one to believe that mannitol is also an active ingredient. The statement should be revised to state "...in single-dose vials containing 3.5 mg bortezomib. Inactive ingredient: 35 mg Mannitol, USP."

2. Under the DOSAGE AND ADMINISTRATION section, the statement "[redacted]" should be revised to state "The recommended dose of VELCADE is 1.3 mg/m^2 administered..."

3. Under the DOSAGE AND ADMINISTRATION section, the statement [redacted] should be moved to the end of the first paragraph [(The recommended dose of VELCADE is 1.3 mg/m^2/dose administered as a bolus intravenous injection twice weekly for two weeks (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12-21).]

4. Under the DOSAGE AND ADMINISTRATION section, third paragraph, the [redacted] abbreviation should not be used. The abbreviated term should be written out.

5. Under the Dose Modification and Reinitiation of Therapy section, terminal zeros should deleted in the statement "[redacted] The terminal zero should also be deleted in the statement contained in Table 9, "[redacted]". Revise throughout the text of the insert.

6. Under the DOSAGE AND ADMINISTRATION, Concomitant Medications, the statement [redacted]

7. Under the DOSAGE AND ADMINISTRATION, Reconstitution/Preparation for Intravenous Administration, the statement [redacted] should be revised to state [redacted]

8. Under the DOSAGE AND ADMINISTRATION, Stability, the phrase [redacted] should be bolded.

IV. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name, Velcade.

This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

B. DDMAC finds the proprietary name, Velcade, acceptable from a promotional perspective.

C. DMETS recommends the above labeling revisions that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

Jennifer Fan, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Denise Toyer, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Denise Toyer
5/12/03 03:08:12 PM
PHARMACIST
Denise Toyer for Jennifer Fan

Carol Holquist
5/12/03 03:23:45 PM
PHARMACIST

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO HFD-420/ODS/PROPRIETARY NAME CONSULTS | FROM: HFD-150/SBRADLEY

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
N03		21-602	NEW NDA	21JAN03

NAME OF DRUG	PRIORITY	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
VELCADE (bortezomib) for INJECTION	CONSIDERATION RUSH	PROTEASOME INHIBITOR	MID-MARCH 2003

NAME OF FIRM: MILLENNIUM PHARMACEUTICALS

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURINGCHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ✗ **ELECTRONIC NDA**
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER (fax)
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY REVIEW
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	OTHER
☐ OTHER	

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below)*
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
DRAFT PACKAGE, IMMEDIATE CONTAINER AND CARTON LABELS WILL BE FORWARDED VIA INTER-OFFICE MAIL

SIGNATURE OF REQUESTER	METHOD OF DELIVERY *(Check one)*
SEAN BRADLEY	✗ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER
	SEAN BRADLEY

/S/

1/15/03

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: Dr. Dan Boring, HFD-530

FROM: Division of: Oncology Drug Products HFD-150
Attention: Chengyi Liang Phone 594-5752

DATE: Jan. 15, 2003

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Velcade™(bortezomib) for Injection

NDA: 21-602

Company Name: Millennium Pharmaceuticals, Inc.

Established name, including dosage form:
Bortezomib 3.5 mg/vials lyophilized

Other trademarks by the same firm for companion products:
N/A

Indications for Use (may be a summary if proposed statement is lengthy):
Relapsed and refractory multiple myeloma.

Initial comments from the submitter: (concerns, observations, etc.)

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Orig. NDA 21-602
HFD-150 Division File
HFD-150/CLiang
HFD-150/RLostritto
HFD-150/SBradley

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved. OMB No 0910-0338
Expiration Date. August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

NDA Number 21-602

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Millennium Pharmaceuticals, Inc.	**May 12, 2003**
TELEPHONE NO *(Include Area Code)* **(617) 679-7000**	FACSIMILE (FAX) Number *(Include Area Code)* **(617) 551-3742**
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: **75 Sidney Street Cambridge, MA 02139 USA**	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE **N/A**

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)*

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
bortezomib	**VELCADE™ for Injection**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
[(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl]boronic acid	**PS-341**

DOSAGE FORM	STRENGTHS:	ROUTE OF ADMINISTRATION:
lyophilized powder for injection	**3.5 mg**	**Intravenous**

(PROPOSED) INDICATION(S) FOR USE:

Relapsed and refractory multiple myeloma

APPLICATION INFORMATION

APPLICATION TYPE *(check one)*

☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION

☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT

☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER (General Correspondence)

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☒ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary) Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND #56,515
MF #12683
MF #1546

This application contains the following items: *(Check all that apply)*	
	1 Index
	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. Financial Information (21 CFR Part 54)
X	20. OTHER *(Specify)* Phase 4 Commitment Letter

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Tanya Lewis	Tanya Lewis, MS Sr. Mgr., Worldwide Regulatory Affairs & Pharmacovigilance	12MAY2003

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
75 Sidney Street Cambridge, MA 02139 USA	(617)551-8951

"MMS <cder.fda.gov>" made the following annotations.

Certificate details:

Display Name:
Tanya Lewis <tlewis@mpi.com>

Certificate Fingerprint:
AD:46:FC:EC:63:F7:6E:AE:61:50:79:0D:06:D4:2A:1A

Certificate Fingerprint:
D6:47:EE:3D:E7:03:A7:15:4F:2E:8C:63:85:D8:E9:49:BD:5E:4C:3D

Certificate Status:
Valid (Direct Trust)

Certificate Issuer:
VeriSign Class 1 CA Individual Subscriber-Persona Not Validated
www.verisign.com/repository/RPA Incorp. By Ref.,LIAB.LTD(c)98
VeriSign Trust Network
VeriSign, Inc.

Certificate Serial Number:
5B:7A:AD:73:A0:ED:56:03:2E:1B:85:DC:0B:33:1E:11

Certificate Validity Period:
Wednesday, December 18, 2002 to Friday, December 19, 2003

The message encryption and/or signature are unacceptable for the following reasons:

The signing certificate is not associated with the sender of the message.

==========

Bradley, Sean

From: Bross, Peter F
Sent: Saturday, May 03, 2003 1:25 PM
): Bradley, Sean
.ubject: FW: Velcade duration of response

For the record...

-----Original Message-----
From: Bross, Peter F
Sent: Saturday, May 03, 2003 1:24 PM
To: 'Lewis, Tanya'; Pietrusko, Robert
Cc: Wang, Yong-Cheng; Farrell, Ann T; Chen, Gang
Subject: Velcade duration of response

Tanya, Bob:

Our statistician, Dr Wang, still reports problems confirming your claimed duration of CR+PR responses in 025:

> I have checked the datasets submitted by the sponsor and
> found that I have the duration of response for Study 024
> only. Can we request the sponsor to submit the duration of
> response for Study 025 and 029 and to explain how they got
> the number 365?

We note your previouls response to this question:

...analyses of duration of response for the 67 patients who responded (CR + PR+ MR) produced a median duration of response utilizing SAS PROC lifetest (Kaplan-Meier analyses) of 365 days. Analysis of the data for the 53 CR/PR patients also produced a median duration of response of 365 days. (See Table 14.2.2A in Section 14.2, Module 5, Section 5.3.5.2.5, M34100-025 CSR, page 574.)

We also note your pooled duration of response KM output, p1783, and table 14.2.2A, attached.

Sponsor's 025 Pooled Duratic
Sponsor's 025 oled Duration .

Can you provide the dataset from which the duration of response output was derived?

When I tried to analyze the duration of CR or PR for 53 patients from IRCRESP dataset, I had to derive the approximate duration of response by the IRC response data by cycle and multiplying cycles by 30/21 to get months. The output looked like it could support labeling for duration of response along the lines of 'at least 5 months, median not reached.'

FDA Duration of CR or PR.doc

Thanks,
-Peter

TELECON MEMO

NDA# 21-602 **Date:** May 02, 2003

Date Received: January 21, 2003 **PDUFA Due Date:** July 21, 2003

Drug Name: Velcade (bortezomib) for Injection

Sponsor: Millennium Pharmaceuticals, Inc.

Proposed Indication: Treatment of Relapsed and Refractory Multiple Myeloma

BETWEEN: Representatives of Millennium Pharmaceuticals, Inc.:

Robert Pietrusko, Pharm.D.	Vice President, Regulatory Affairs
John Bishop, PhD	Associate Director, Process Development, Small Molecule Manufacturing
Jennifer Smith, PhD	Senior Process Engineer, Small Molecule Manufacturing
Suhe Chen, PhD	Senior Manger, Analytical Development
Marc Wolfgang, MS	Associate Director, Quality Control
Melody Brown, BS	Director, CMC, Worldwide Regulatory Affairs
Colleen Costello, PhD	Associate Director, Regulatory
Anne Randolph, PhD	VP, QA
Fraser MacDonald, PhD	Sr. Director, QC/AD
Fraser Pickersgill, PhD	Sr. Manager, Process Development
Poh Hui, PhD	Director, Technical Operations

AND

Rik Lostritto, PhD	CMC Team Leader
Chengyi Liang, PhD	CMC Reviewer
Sean Bradley, RPh,	Consumer Safety Officer

4 PAGE (S) WITHHELD

MEMORANDUM OF TELECON

DATE OF TELECON: April 17, 2003 **Time:** 1:30 PM, EST

APPLICATION NUMBER: 21-602

BETWEEN: Dr. Harvey Katzen

AND

Richard Pazdur, MD, Director
Ann Farrell, MD, Acting Team Leader
Peter Bross, MD, Medical Reviewer
Robert Kane, MD, Medical Reviewer
Sean Bradley, RPh, Consumer Safety Officer

SUBJECT: Approval of Velcade (bortezomib) Injection, NDA 21-602

BACKGROUND: A medical background package was forwarded to Dr. Katzen for his review prior to the teleconference.

DISCUSSION:

On April 14, 2003, the medical review team called Dr. Katzen to discuss response rates, current clinical experience and safety data for Velcade.

Dr. Pazdur briefly summarized the contents of the application and stated that the Division was pursuing accelerated approval of this NDA and requested Dr. Katzen's opinion of the Division's planned action.

Dr. Katzen agreed with the Division's decision to approve this NDA under subpart H and stated that this drug offers patients a better treatment option compared to current therapies in this setting.

/S/
Sean Bradley, R.Ph.
Consumer Safety Officer

MEMORANDUM OF TELECON

DATE OF TELECON: April 14, 2003 **Time:** 5:30 PM, EST

APPLICATION NUMBER: 21-602

BETWEEN: Dr. Chatchada Karanes

AND

Richard Pazdur, MD, Director
Grant Williams, MD, Deputy Director
Ann Farrell, MD, Acting Team Leader
Peter Bross, MD, Medical Reviewer
Robert Kane, MD, Medical Reviewer
Sean Bradley, RPh, Consumer Safety Officer

SUBJECT: Approval of Velcade (bortezomib) Injection, NDA 21-602

BACKGROUND: A medical background package was forwarded to Dr. Karanes for her review prior to the teleconference.

DISCUSSION:

On April 14, 2003, the medical review team called Dr. Karanes to discuss response rates, current clinical experience and safety data for Velcade.

Dr. Pazdur briefly summarized the contents of the application and stated that the Division was pursuing accelerated approval of this NDA and requested Dr. Karanes' opinion of the Division's planned action.

Dr. Karanes agreed with the Division's decision to approve this NDA under subpart H and stated that this drug looks to be better than current therapies.

/S/
Sean Bradley, R.Ph.
Consumer Safety Officer

MEMORANDUM OF TELECON

DATE OF TELECON: April 14, 2003 **Time:** 4:15 PM, EST

APPLICATION NUMBER: 21-602

BETWEEN: Dr. Bruce Cheson

AND

Richard Pazdur, MD, Director
Grant Williams, MD, Deputy Director
Ann Farrell, MD, Acting Team Leader
Peter Bross, MD, Medical Reviewer
Robert Kane, MD, Medical Reviewer
Sean Bradley, RPh, Consumer Safety Officer

SUBJECT: Approval of Velcade (bortezomib) Injection, NDA 21-602

BACKGROUND: A medical background package was forwarded to Dr. Cheson for his review prior to the teleconference.

DISCUSSION:

On April 14, 2003, the medical review team called Dr. Cheson to discuss response rates, current clinical experience and safety data for Velcade.

Dr. Pazdur briefly summarized the contents of the application and stated that the Division was pursuing accelerated approval of this NDA and requested Dr. Cheson's opinion of the Division's planned action.

Dr. Cheson agreed with the Division's decision to approve this NDA under subpart H and stated that this is an exciting drug.

/S/
Sean Bradley, R.Ph.
Consumer Safety Officer

MEMORANDUM OF TELECON

DATE OF TELECON: April 11, 2003 **Time:** 5:00 PM, EST

APPLICATION NUMBER: 21-602

BETWEEN: Dr. Donna Przepiorka

AND

Richard Pazdur, MD, Director
Grant Williams, MD, Deputy Director
Ann Farrell, MD, Acting Team Leader
Peter Bross, MD, Medical Reviewer
Robert Kane, MD, Medical Reviewer

SUBJECT: Approval of Velcade (bortezomib) Injection, NDA 21-602

BACKGROUND: A medical background package was forwarded to Dr. Przepiorka for her review prior to the teleconference.

DISCUSSION:

On April 14, 2003, the medical review team called Dr. Przepiorka to discuss response rates, current clinical experience and safety data for Velcade.

Dr. Pazdur briefly summarized the contents of the application and stated that the Division was pursuing accelerated approval of this NDA and requested Dr. Przepiorka's opinion of the Division's planned action.

Dr. Przepiorka agreed with the Division's decision to approve this NDA under subpart H and stated that based on the response rate, complete or partial, this drug has the ability to have clinical benefit in refractory myeloma patients.

/S/
Sean Bradley, R.Ph.
Consumer Safety Officer